Resting-state electroencephalogram in learning-disabled children: power and connectivity analyses

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Resting-state electroencephalogram in learning-disabled children: power and connectivity analyses

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The neurophysiological underpinnings of learning disabilities remain unknown. In this clinical study, we recorded electroencephalograms for a large sample of children with learning disabilities (LD) and healthy control children ($n = 216$) during resting states in which the eyes were either open or closed. We calculated the power and lagged phase coherence in six main frequency bands (delta, theta, lower and upper alpha, and lower and upper beta) to re-evaluate the question of whether children with LD show frontal theta power increases and posterior alpha band decreases on the basis of patterns of electroencephalogram oscillation, which could then be considered as evidence for the so-called 'maturational delay hypothesis.' We identified a general (not restricted to frontal electrodes) power increase in the theta band and no accompanying concomitant alpha band decrease at the posterior electrode position. In addition, we observed increased beta band power at frontal electrodes for LD children. With respect to lagged phase coherence, which is a coherence measure not influenced by volume conduction, we identified decreased coherence for children with LD in the upper alpha band during the eyes closed condition. We interpret this LD-specific resting-state activation pattern as indicating a suboptimally functioning neural resting-state network that provides a detrimental 'starting point' for task-specific brain activations. *NeuroReport* **00:000–000**

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Keywords: beta band power, brain maturation, children, electroencephalogram, lagged phase coherence, learning disability, theta band power

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Introduction

Learning disabilities (LD) are frequently observed problems in young children that hinder their academic achievements. Because LD has been acknowledged as a major problem, particularly when these children enter school, interest in studying the psychological and neurophysiological underpinnings of this disability has increased in the past few decades. Several studies using functional MRI, structural MRI, and electroencephalogram (EEG) measurements have reported on the neurophysiological and neuroanatomical characteristics of children suffering from specific variants of LD [1–5]. Although these studies have furthered our understanding of the neurophysiological and neuroanatomical origins of LD, identification of objective neurophysiological biomarkers in a more clinical and mobile context is required. If such standard measures are established, large-scale studies can be carried out that will help to delineate specific LD subgroups and develop new tools for LD diagnosis and treatment.

For this, EEG measurements have been used in several studies to provide a more mobile neurophysiological measurement. EEG studies that examined children with LD have shown that they have greater theta and less alpha (and beta) power than what is normal for their age during a relaxed state. These findings are often considered evidence for the so-called 'maturational delay hypothesis' [6–14]. This knowledge has been used to guide a specific neurofeedback therapy that supports the improvement of LD disabilities [15].

Although most EEG studies are based on 'classical' EEG power analyses, only a few studies have focused on functional connectivity measures. Using a relatively large sample of children with LD, Gasser *et al.* [10] did not identify considerable coherence differences between children with LD and healthy control (HC) children. Marosi *et al.* [11,12], who tested children with mild and severe reading and writing problems, used coherence measures for the different frequency bands on the basis of the EEG waveforms. In fact, they identified decreased coherences between frontal electrodes in the theta and alpha bands, suggesting that the frontal areas are less strongly functionally connected in children with LD.

In this study, we re-evaluate the neurophysiological underpinnings of LD in a large sample of children with a cultural background that has received little attention, namely, Saudi Arabia. Because it has been shown that

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LD diagnosis strongly depends on the cultural background and socioeconomic class of the examined children [16], we aimed to examine whether the same findings obtained in Western children with LD could also be obtained for Saudi Arabian children. In this new large-scale study, we aimed to examine the following five questions: (i) Do we find the same increase in theta band power and decrease in alpha band as reported in previous studies? (ii) Are these theta and alpha band features found locally (e.g. only frontal or parietal) or are they distributed (e.g. general increase or decrease)? Several previous studies argue that theta band increases are found in frontal electrode locations, whereas alpha-band power decreases are found prominently in posterior locations. (iii) Are the lower and upper alpha bands similarly affected in children with LD? Most previous EEG studies on children with LD did not explicitly distinguish between both alpha bands. However, new brain-imaging and EEG studies have shown that the alpha band is not a homogeneously reacting frequency band because the lower (8–10 Hz) and upper (10–12 Hz) alpha bands often dissociate in terms of their involvement in cognition and attention. Although the lower alpha band is suggested to be primarily involved in the control of attentional demands, upper alpha-band oscillation has been observed consistently during long-term memory processes [17]. (iv) Are the resting-state EEG features obtained under conditions of eyes open (EO) and eyes closed (EC) similar in children with LD? Most previous studies on EEG resting states in children with LD did not distinguish between these states. However, some studies have shown that the EC and EO resting states are of low and high arousal, respectively [18]. In addition, it has been shown that intracortical connectivities are different for EO and EC conditions [19,20]. Thus, the specific resting-state features of children with LD may be influenced by the underlying arousal or specific mindsets operative during resting state. (v) Because EEG coherences have rarely been measured in children with LD, the question arises of whether EEG coherence, particularly in the theta and alpha bands, is different in children with LD compared with those who are well developed? Classical EEG coherence measures obtained with EEG have the limitation of volume conduction or common sources, which might lead to spurious correlations between the time series recorded from nearby electrodes. One possible means of overcoming this problem is to apply the rarely used measure of lagged phase coherence, which measures nonlinear connectivities and reflects 'true' physiological connectivity independent of volume conduction [21–23]. On the basis of earlier findings in children with LD, the working hypothesis is that during resting state, the functional connectivity would be different (most likely diminished) in children with LD compared with HCs, particularly in the slow frequency bands for which children with LD mostly show increased power values.

Participants and methods

Participants

This study is based on a sample including a total of 216 children. Data from 54 children with LD and 32 HCs were used in two previous papers of our group [13,24]. This increased sample comprised 132 healthy controls (29 girls and 103 boys, mean age ± SD for boys: 10 ± 1.2, girls 9.8 ± 1.6) and 84 children with LD (boys: 9.6 ± 1.6, girls: 9.9 ± 1.3). Children with LD were diagnosed and classified according to standard tests used by the Ministry of Education of Saudi Arabia (*https://www.moe.gov.sa/Arabic/Pages/default.aspx*), which were guided by the criteria provided by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (DSM-IV). The IQ scores of the children with LD were at least greater than 85, with a mean IQ of 89.8 (SD = 11.5). School performance of all children with LD was at least 1 school grade below the normal grade level. The HC children performed at least on average in all tests and they were enrolled in the age-appropriate grade level. They had an average IQ (mean = 99.3, SD = 2.5). Children with LD and HC differed significantly in terms of the IQ measurements [*t*-test: $t(111.91) = 14.5$, $P < 0.0001$]. All children (LD and HC) did not suffer from neurological, psychiatric, and other health issues. Children with ADHD were excluded. Thus, the classification criteria conformed to the criteria used by Fernández *et al.* [15] and conformed to the regulations of the Ministry of Education of Saudi Arabia. All children were right-handed according to self-report and a short writing test. The study complied with the Ethical Principles for Medical Research Involving Human Subjects established by the Declaration of Helsinki. All the children were volunteers, and informed consents from the parents were obtained for all study participants.

Eelectroencephalogram recording, data acquisition, analysis, and functional coherence

EEG was recorded in EC and EO resting-state conditions, at least 2 min for every period. Participants had to sit still and try not to blink or move their eyes. EEG was recorded using the BEE Medic x23 system (BEE Medic GmbH, Kirchberg, St. Gallen, Schweiz) with 19 silver-chloride electrodes fixed to the scalp according to the international 10–20 system using ElectroCaps (*http://www.hbimed.com/de/qeeg/shop/qeeg-systeme/elektro-cap-set-ii.html*). The EEG signals were referenced to linked ears, filtered between 0.5 and 50 Hz, and digitized at a rate of 500 Hz. The ground electrode was placed on the forehead, with all electrode impedances maintained below 5 kΩ. For artifact correction and preprocessing, WinEEG software (*http://www.mitsar-medical.com/eeg-software/qeeg-software/download.html*) was used. We used the same artifact-correction strategy as that used in a previous paper of our group [25], which we, therefore, describe only briefly. Known artifacts (eye movements and typical EMG artifacts) were corrected by zeroing the activation curves of individual independent component analysis [26]. In addition, epochs with an excessive amplitude of

filtered EEG and/or excessive faster and/or slower frequency activity were automatically marked and excluded from further analysis. The exclusion thresholds were set as follows: (a) 100 μV for nonfiltered EEG; (b) 50 μV for slow waves in the 0–1 Hz band; and (c) 20 μV for fast waves filtered in the 20–35 Hz band. For EEG data analysis, not less than 30 artifact-free EEG epochs were used (around 60 s). There was no between-group difference in terms of artifact-contaminated rejected EEG epochs ($P > 0.3$). Spectral analysis was carried out for the raw (common average montages) EEG recordings using the WinEEG software. For each individual, each electrode position and condition power spectra were computed. For this, artifact-free continuous EEG was divided into 4.096 s epochs using a Hanning time window (epochs overlapped by 50%) and subjected to Fast Fourier Transform. The grand average power spectra were computed for each EEG channel, for each group (HC and LC children), and for the EO and EC conditions separately. The absolute power was computed for the delta (2–4 Hz), theta (4–8 Hz), lower alpha (8–10 Hz), upper alpha (10–12 Hz), lower beta (13–20 Hz), and upper beta (20–30 Hz) frequency bands.

Statistical analysis of spectral power and lagged phase coherence

The spectral power values (μV^2) were collected for all frequency bands and electrodes and stored as ASCII files for further statistical analysis. Lagged phase coherences were computed separately for each frequency band across all electrodes using the WinEEG software. As we used 19 electrodes, the total number of the coherences obtained sums up to 171 coherences for each frequency band ($19 \times 18/2 = 171$). The spectral power values were log transformed to stabilize the variances and subjected to a repeated-measures analysis of variance (rANOVA) separately for each frequency band. In these analyses, the following factors were used: (i) RS = resting-state condition (EC vs. EO), (ii) electrodes = the 19 electrodes, and (iii) group = LD versus HC. We calculated for each frequency band one rANOVA using the afex R package [27]. Effect sizes in the context of the rANOVAs are given using the generalized η^2 as recommended for a repeated-measures design [28]. For the analysis of connectivity measures, we calculated the mean connectivity across all 171 connectivity measures separately for each frequency band. These connectivity measures were subjected to the rANOVAs using the afex package with the following factors: (i) RS = resting-state condition (EC vs. EO), (ii) frequency band = the six frequency bands, and (iii) group = LD versus HC. We did not use sex as a further variable as the sample size for girls and boys differed considerably, resulting in an extremely unbalanced design, preventing us from drawing firm conclusions in case of significant sex-related interactions. For the rANOVAs, we applied a significance threshold of P equal to 0.01 to conform to the need to perform conservative statistical testing that is necessary because of the relatively large sample size.

Results

Spectral data

The results of the rANOVAs are summarized in Table 1. For four of the six frequency bands, we found significant three-way 'Group × Electrodes × RS' interactions [delta: $F(5.9, 1261.9) = 3.9$, $P < 0.0009$, generalized $\eta^2 = 0.001$; theta: $F(7.6, 1620.5) = 3.9$, $P < 0.00002$, generalized $\eta^2 = 0.0009$; lower beta: $F(8.45, 1807.6) = 4.5$, $P < 0.0001$, generalized $\eta^2 = 0.001$; upper beta: $F(8.64, 1796.0) = 3.71$, $P = 0.0002$, generalized $\eta^2 = 0.001$]. These three-way interactions were all small, associated with small generalized η^2 values, and were mainly qualified by different between-group differences for the different electrodes and the different RS conditions. As can be seen in Fig. 1 (and that was confirmed by subsequently performed post-hoc tests), the between-group differences are slightly stronger at frontal electrodes for all of these frequency bands with slightly stronger differences during the EO condition.

There were also significant two-way 'Electrodes : RS' interactions, significant 'RS' main effects, and 'Electrodes' main effects, which were not of interest for our project and reflected known effects (e.g. stronger alpha band power during the EC condition at posterior electrodes). We were mainly interested in main effects and interactions where the 'Group' effect (here the difference between LD and HC) was involved. One two-way 'Group : RS' interaction was found for the upper beta band [$F(8.6, 1849.12) = 4.4$, $P < 0.0001$, generalized $\eta^2 = 0.01$], which was indicated by stronger upper beta power for LD than HC children during the EO condition. In addition, there were four two-way 'Group : Electrodes' interactions [delta: $F(18.5, 1820.9) = 3.9$, $P = 0.0001$, generalized $\eta^2 = 0.005$; theta: $F(10.10, 2160.3) = 2.6$, $P = 0.004$, generalized $\eta^2 = 0.003$; lower beta: $F(9.6, 2045.1) = 2.6$, $P < 0.0001$, generalized $\eta^2 = 0.006$; upper beta: $F(8.6, 1849.1) = 6.8$, $P < 0.0001$, generalized $\eta^2 = 0.01$] that were indicated by slightly larger group differences at the frontal and occipital electrodes. Post-hoc tests for the theta band showed stronger theta band power for the LD children compared with the HC children for all electrodes.

The strongest effects were found for the main effect 'Group' showing stronger power values for the LD versus HC children for three frequency bands [theta: $F(1, 214) = 31.8$, $P < 0.0001$, generalized $\eta^2 = 0.09$; lower alpha: $F(1, 214) = 8.8$, $P = 0.003$, generalized $\eta^2 = 0.03$; upper beta: $F(1, 214) = 7.9$, $P = 0.005$, generalized $\eta^2 = 0.02$]. The strongest effect (generalized $\eta^2 = 0.09$) was found for the theta band (Fig. 2).

Coherence data

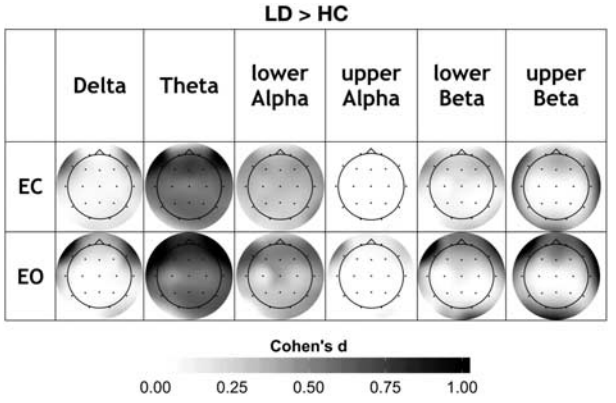
The rANOVAs for the lagged phase coherences showed two-way interactions for 'Group × Frequency Band' [$F(2.30, 467.64) = 4.58$, $P = 0.008$, generalized $\eta^2 = 0.003$], 'Group × RS' [$F(1, 203) = 5.37$, $P = 0.02$, generalized $\eta^2 = 0.009$], and 'Frequency band × RS' [$F(2.05, 415.43) = 54.06$, $P < 0.0001$, generalized $\eta^2 = 0.02$]. The 'Group × Frequency Band' interaction is shown in Fig. 3.

Table 1 Summary of the 2 × 2 × 19 repeated-measures analyses of variance

	Delta	Theta	Lower alpha	Upper alpha	Lower beta	Upper beta
Group	–	< 0.0001	0.003	–	–	0.005
Electrodes	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Group : electrodes	0.001	0.004	–	–	< 0.0001	< 0.0001
RS	0.0002	< 0.0001	< 0.0001	< 0.0001	< 0.0001	0.01
Group : RS	–	–	–	–	–	0.01
Electrodes : RS	< 0.0001	< 0.0001	< 0.0001	< .0001	< 0.0001	< 0.0001
Group : electrodes : RS	0.0009	0.0002	-	-	< 0.0001	< 0.0001

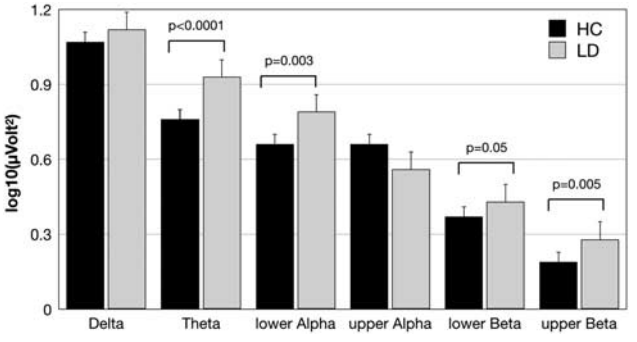
The P values for effects passing the $P \leq 0.01$ threshold are shown. Effects in which we are specifically interested in this study are underlined and comprise all effects involving the 'Group' factor.
RS: EC versus EO; group: LD versus HC; electrodes: 19 electrodes.
EC, eyes closed; EO, eyes open; HC, healthy control; LD, learning disabled; RS, resting state.

Fig. 1



Topolpots showing the LD > HC differences as Cohen's d values [29] separately for the six frequency bands. The dark gray marked locations indicate at least moderately strong LD > HC differences ($d > 0.5$). The strongest differences were found for the theta band at all electrodes. HC, healthy control; LD, learning disabled.

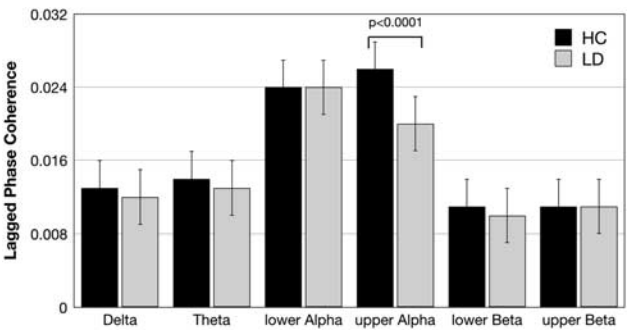
Fig. 2



Mean log power values and 95% confidence intervals broken down for the two groups and the six frequency bands. HC, healthy control; LD, learning disabled.

As can be seen from this figure (and from additionally performed post-hoc tests), HC children showed stronger lagged phase coherences for the upper alpha band. The 'Group × RS' interaction was indicated by larger

Fig. 3



Mean lagged phase coherence and the 95% confidence intervals broken down for the LD and HC children and the six frequency bands. HC, healthy control; LD, learning disabled.

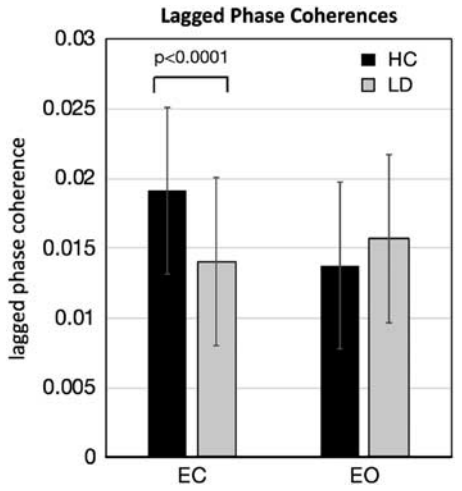
coherences for the HC children, especially during the EC condition (Fig. 4). The main effect 'Frequency Band' depends on the larger coherences for both alpha bands [$F(2.3, 467.64) = 122.4$, $P < 0.0001$, generalized $\eta^2 = 0.08$].

Discussion

Our study was guided by five study questions: (i) Is there an increase in theta band power and a concomitant decrease in alpha band power in children with LD? (ii) Are these theta and alpha band respective power increases and decreases found locally or are they distributed over the entire scalp? (iii) Are the lower and upper alpha bands different in children with LD? (iv) Do specific between-group differences exist under EO and EC conditions? (v) Do children with LD and HC differ in terms of the obtained coherence measures and, if so, in which frequency band can this coherence be detected?

We found stronger power values in children with LD for the theta, lower alpha, lower beta, and upper beta bands, whereas there was no power decrease for both alpha bands. The strongest between-group difference was found for the theta band. Thus, this finding corresponds to several previously published studies showing an increase in theta band power in children with LD [6–14]. However, unlike in several previous studies, we did not observe a decrease in alpha band power. Instead, we

Fig. 4



Mean lagged phase coherence and the 95% confidence intervals broken down for the LD and HC children and the EC and EO resting-state conditions. EC, eyes closed; EO, eyes open; HC, healthy control; LD, learning disabled.

identified a slight increase in power in the lower alpha band, whereas the power of the upper alpha band was more or less similar for the children with LD and HC. Thus, our findings do not support the 'maturation delay hypothesis,' which suggests an increase in frontal theta power accompanied by a considerable decrease in posterior alpha and beta band power. Although the theta band increases for children with LD were found to occur more strongly at frontal electrode positions, these increases were distributed across the entire set of 19 electrodes and included frontal as well as posterior locations. Thus, the increases in theta band were found across the entire scalp.

The role of theta band oscillations has been addressed primarily in the context of cognitive functions such as learning and memory [17,30]. Increased tonic theta spectral power, particularly when it is measured during resting states, is a nonspecific feature of many disease and abnormal states associated with impaired cognitive functions. Generally increased theta band power is associated with a low level of cortical activation, most likely induced by decreased depolarizations of thalamocortical afferents connecting with apical dendrites of cortical neurons. This kind of distributed theta band power increase (here even abnormally high) is often observed in patients with acquired dementias, typically Alzheimer's disease, and also in developmental conditions such as nonspecific mental retardation and attention deficit hyperactivity disorder [31–34]. Thus, we interpret the increased theta band power found in the children with LD as indicating a suboptimally activated cortical resting-state network. Because resting-state network activation can be interpreted as a kind of starting point for neural activations and demanding cognitive processes, one can assume that children with LD initiate their task-related networks from an inefficient suboptimal activation level [35].

This abnormal increase in tonic theta band has to be distinguished from the local frontal midline theta band oscillation, which represents neural activity from frontostriatal circuits including the lateral prefrontal cortex, the cingulum, the basal ganglia, and the thalamus. This system is specifically activated during the performance of ongoing tasks, particularly when workload or mental load increases [36,37]. However, the participants in our study showed an abnormal increase in tonic theta band oscillations, which points to a general tonic cortical activation deficiency even during rest.

Unexpectedly, we found stronger lower and upper beta band power in LD children mostly at frontal electrodes. Abnormally increased beta band power, especially at frontal electrode positions, has been reported for adult alcoholics [38], adult patients with panic disorders and agoraphobia [39], and older adults with cognitive decline [40]. Increased beta band power (at frontal electrodes) has also been reported after the administration of ethanol [41]. Abnormal beta band power is often considered a neurophysiological index of (abnormal) cortical hyperexcitability and disinhibition [42], which might indicate a deteriorated balance of inhibition and excitation in maintaining cortical homeostasis. According to Engel and Fries [43], increased beta band power can also be considered an 'abnormal persistence of the status quo and a deterioration of flexible behavioral and cognitive control.' On the basis of the above-mentioned explanations of abnormally increased beta band power, we speculate that LD children might show cortical hyperexcitability and disinhibition associated with a deterioration in flexible behavioral and cognitive control.

We found weaker lagged phase coherence in children with LD for the upper alpha band. Thus, children with LD show stronger general theta band power and stronger local beta band power, but decreased upper alpha band coherence. This decreased coherence was only found during the EC condition, for which arousal is known to be low [18]. The lower lagged phase coherence in children with LD for the upper alpha band is a new finding and has not been reported in previous studies. Because this is the first report describing decreased alpha band lagged phase connectivity in children with LD, we refrain from making too strong conclusions. Nevertheless, the alpha band activity is linked strongly to cortical inhibition [44]. Thus, one might speculate that children with LD have a lower degree of distributed and orchestrated cortical inhibition, which might hamper the activation of networks associated with the control of cognitive functions. Together with the general theta band and local beta band power increase, this

degraded coherence might indicate a suboptimally active resting-state network.

Only three studies have examined EEG coherence in children with LD. These studies have uncovered different findings. Gasser *et al.* [10] reported no clear results for coherence measures in children with LD. Marosi *et al.* [11,12] identified decreased coherence in the theta and alpha bands. However, it must be mentioned that these authors used total coherence measures on the basis of surface EEG oscillations. These coherence measures are strongly contaminated by volume conduction. Thus, relating these findings to our results is difficult, if not impossible. Future studies that use more sophisticated coherence measures (e.g. intracortical coherence measures) in different samples might help to elucidate the specific patterns of LD-related functional coherence.

Limitations of this study

This study has several limitations. First, this is a clinical study with a specific population. Thus, despite the fact that our sample is large, we could not collect sufficient data to construct a well-balanced design to enable the study of sex differences. It was also necessary to keep the burden of examining children as low as possible. Therefore, we performed only relatively short resting-state measurements with a clinical EEG system consisting of only 19 electrodes. Second, considering the nature of our study, the children who participated in our study were all from Saudi Arabia. It remains unclear whether their cultural background had an influence on cortical oscillations. In a previous study, we found some differences between Saudi Arabian and Swiss children [25]. In this respect, we must exercise caution when generalizing our results to children with LD from different cultures. In addition, the existence of special but unknown cultural influences that lead to LD diagnosis in the children whom we examined cannot be ruled out. Furthermore, it should be kept in mind that the criteria used to diagnose LD in Saudi Arabian children are still based on partly outdated criteria of the DSM-IV.

Conclusion

We identified stronger theta band power (at all electrodes), a lower degree of phase lagged coherence for the upper alpha band, and an increased beta band power at frontal electrodes in children with LD. This LD-specific resting-state activation pattern points to three deficient neurophysiological activation features, which, even when observed alone, are associated with cognitive deficits and several disease states. In our study, these specific neurophysiological features were observed in combination: (i) lower and thus suboptimal cortical activation (indicated by abnormally strong theta band oscillation), (ii) deteriorated homeostasis between cortical inhibition and excitation (indicated by abnormally high frontal beta band oscillation), and (iii) diminished functional connectivity for a neural network associated with cortical inhibition. This abnormal pattern of tonic neurophysiological activity represents a suboptimal neural starting point for task-specific brain activations. Thus, LD children require more arousal and cortical activation to trigger selective attention and cortical top-down control, and to activate higher-order cognitive processes (e.g. working memory).

These brain activation features may be used as target features for diagnosing and curing LD. One approach could be to train children to reduce their extensive theta and beta band activity and to increase their functional connectivity for the upper alpha band. The first attempts to train children with LD were made successfully using EEG-based neurofeedback approaches [14]. The participants in this neurofeedback study were trained to reduce the theta/alpha ratio of the ongoing EEG. Future neurofeedback interventions should also focus on techniques to improve functional connectivities as we have suggested in a previous paper [45]. Perhaps the combined training of spectral and coherence features could be a more fruitful approach to improve the suboptimal resting-state network in LD children. A further possible intervention could be the application of short repetitive transcranial stimulation over different scalp locations to inhibit theta band activity or to induce faster oscillations. Although this has not been applied in the context of LD rehabilitation, it has been shown repeatedly that it is possible to induce particular EEG oscillation patterns by applying short bursts of repetitive transcranial stimulation pulses at different scalp locations [46]. More important, however, is the identification of a suboptimal neural activation pattern, which points to an abnormal and thus suboptimal resting-state network, which may be one of the reasons for the LD-specific behavioral and cognitive deficits.

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Conflicts of interest

There are no conflicts of interest.

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